PATENT COOPERATION TREATY



# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| F16536 CPF | | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/IB 02/01554 | 08.05.2002 | 12.04.2002 |

International Patent Classification (IPC) or both national classification and IPC

C07C51/41

Applicant

TECHNICAL AND COMMERCIAL SERVICES INTERNATIONAL ..

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 18.09.2003 | -1 1. 11. 04 |

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/01554

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

| | |
|---|---|
| 2-28 | as originally filed |
| 1, 1a | filed with telefax on 19.04.2004 |

**Claims, Numbers**

| | |
|---|---|
| 1-18 | filed with telefax on 19.04.2004 |

**Drawings, Sheets**

| | |
|---|---|
| 1/3-3/3 | as originally filed |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-18 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-18 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-18 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

The present set of claims has been amended so as to include the reaction time in the first reactor. This is supported by the subject-matter of claim 2 as filed.

The following documents are referred to :

D1: US-A-4335257
D2: US-A-2396115
D3: WO-A-0232235
D4: US-A-470000

The present application concerns a process for making acid salts, which differs from the processes of the documents D1-D4 by the fact that the reaction slurry is transferred into a second reaction vessel and by the fact that the reaction time in the first reactor is controlled so as to stay within 3 and 180 seconds.

The inventiveness of the present application can rely on the fact that it is not obvious to design a 2 pot process for making carboxylic acid salt, while adjusting the reaction time within both reactors so as to have a maximum amount of water in the reaction mixture. The advantages obtained by this process (see page 28) are unexpected by the skilled person.

Further remarks :
In order to comply with the requirements of rule 5.1.ii PCT, the most relevant prior art should be cited and briefly discussed.

# A METHOD OF MAKING SALT

THIS INVENTION relates to a method of making a salt.

The metal salts of lower molecular mass acids such as substituted and unsubstituted $C_1$ - $C_{10}$ acids, aromatic carboxylic acids of the formula Ph-$(CH_2)_x$-$CO_2H$ where x is 0 - 4, benzoic acid and phenylacetic acid are typically made by reacting the acid with a basic salt of the metal such as its hydroxide or carbonate. In some cases, the reactions are conducted in a relatively dilute aqueous medium and isolation of the salt of the acid requires removal of excess water and a drying step. In other cases, the acid is added to a slurry of a base such as calcium carbonate or calcium hydroxide in a closed vessel. The slurry then progressively thickens and passes through a "plastic" stage after which it is dried. Handling the product after the plastic stage is generally difficult. Furthermore large scale production process drying is energy intensive and expensive. It is an object of the invention to address these problems.

A related process for the preparation of the calcium salt of 2-hydroxy-4-thiomethylbutyric acid is described in PCT/IB01/02087.

According to a first aspect of the invention, there is provided a method of making the salt of an acid selected from $C_1$ - $C_{10}$ carboxylic acids, aromatic carboxylic acids of the formula Ph-$(CH_2)_x$-$CO_2H$ where x is 0 - 4, and glycerophosphoric acid, the method including the steps of

combining and mixing the acid and a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium, or a mixture of any two or more thereof, in a first reaction zone, the combining and mixing step being carried out over a first period to produce a reaction mixture in the first reaction zone;

transferring the reaction mixture at the end of the first period from the first reaction zone to a second reaction zone the transferring step being carried out over a second period; and

allowing heat generated by reaction between the acid and the base in the

1. A method of making the salt of an acid selected from $C_1$ - $C_{10}$ carboxylic acids, aromatic carboxylic acids of the formula Ph-$(CH_2)_x$-$CO_2H$ where x is 0 - 4, and glycerophosphoric acid, the method including the steps of

combining and mixing the acid and a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium, or a mixture of any two or more thereof, in a first reaction zone, the combining and mixing step being carried out over a first period of 3 – 180 seconds to produce a reaction mixture in the first reaction zone;

transferring the reaction mixture at the end of the first period from the first reaction zone to a second reaction zone the transferring step being carried out over a second period; and

allowing heat generated by reaction between the acid and the base in the second reaction zone to drive off sufficient water to produce a product mixture containing less than about 8% (m/m) water, provided that the acid is not 2-hydroxy-4-thiomethylbutyric acid.

2. A method as claimed in Claim, in which the second period is 2 - 60 seconds.

3. A method as claimed in Claim 1, in which the combining step takes about 2 - 60 seconds.

4. A method as claimed in Claim 2, in which the first period is 3 - 60 seconds.

5. A method as claimed in any one of Claims 2 to 4 inclusive, in which the second period is 3 - 30 seconds.

6. A method as claimed in any one of the preceding claims, in which the carboxylic acid is a substituted or an unsubstituted $C_1$ - $C_{10}$ acid.

7. A method as claimed in any one of Claims 1 to 6 inclusive, in which carboxylic acid is monocarboxylic acid selected from formic acid, acetic acid, propanoic acid, butanoic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid and their alkylated or hydroxylated analogues.

8. A method as claimed in any one of Claims 1 to 6 inclusive, in which the carboxylic acid is a dicarboxylic acid selected from oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sibaccic acid and their unsaturated, alkylated or hydroxylated analogues.

9. A method as claimed in any one of Claims 1 to 5 inclusive, in which the acid is benzoic acid or phenylacetic acid.

10. A method as claimed in any one of the preceding claims, in which the acid is in the form of an aqueous solution.

11. A method as claimed in Claim 10, in which the aqueous solution has a concentration of about 60 - 99,5% by mass of the acid.

12. A method as claimed in any one of the preceding claims, which includes allowing the heat generated to drive off sufficient water to produce a product mixture containing less than about 2,5% water.

13. A method as claimed in any one of Claims 10 to 12 inclusive, which includes the prior step of warming the solution of acid to 50 - 96°C.

14. A method as claimed in any one of the preceding claims, which includes the further steps of successively combining and mixing a plurality of batches of the acid and base with water in the first reaction zone to produce successive batches of the reaction mixture and successively transferring each of the batches to the same second reaction zone.

15. A method as claimed in any one of the preceding claims which includes agitating the reaction mixture in the second reaction zone.

16. A method of making salt of an acid selected from $C_1$ - $C_{10}$ carboxylic acids, aromatic carboxylic acids of the formula Ph-$(CH_2)_x$-$CO_2H$ where x is 0 - 4, benzoic acid, and glycerophosphoric acid, the method including the steps of

combining and mixing the acid, a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium, or a mixture of any two or more thereof and water in a first reaction zone to produce a reaction mixture in the first reaction zone;

continuously transferring the reaction mixture from the first reaction zone to a second reaction zone, the reactants being added to the first reaction zone in successive batches and the reaction mixture being continuously removed from the first reaction zone at a rate which is selected so that the residence time of the reaction mixture in the first reaction zone is between about 1 and 180 seconds; and

allowing heat generated by reaction between the acid and the base in the second reaction zone to drive off sufficient water to produce a product mixture containing less than about 8% water,

provided that the acid is not 2-hydroxy-4-thiomethylbutyric acid.

17. A method as claimed in Claim 16 which the heat generated is allowed to drive off sufficient water to produce a product mixture containing less than about 2,5% water.

18. A continuous method of making a salt of an acid selected from $C_1$ - $C_{10}$ carboxylic acids, aromatic carboxylic acids of the formula Ph-$(CH_2)_x$-$CO_2H$ where x is 0 - 4, and glycerophosphoric acid, the method including the steps of

simultaneously feeding, into a reaction zone, an aqueous solution of the acid, and a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium or a mixture of any two or more thereof to produce a reaction mixture in the reaction zone; and

a rate which is selected so that the residence time of the reaction mixture in the reaction zone is 3 – 180 seconds and is sufficient to initiate reaction between the acid and the base but not sufficient to drive off water from the reaction mixture and allowing heat generated by further reaction between the acid and the base in the second zone to drive off sufficient water to produce a product mixture containing less than about 8% water, provided that the acid is not 2-hydroxy-4-thiomethylbutyric acid.